

Visual Prognosis after Explantation of a Corneal Shape-Changing Hydrogel Inlay in Presbyopic Eyes

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ABSTRACT

The purpose of this case series is to report visual outcomes in patients who underwent explantation of the Raindrop® hydrogel corneal inlay. Retrospective chart review comprising four cases of explantation of the Raindrop® corneal shape-changing hydrogel inlay: pre-implantation, pre-explantation, and post-explantation values for uncorrected distance visual acuity, uncorrected near visual acuity, and corrected distance visual acuity (CDVA) were measured; keratometric and tomographic data were collected using the Pentacam system (Oculus, Inc). Three eyes were explanted for progressive haze after implantation that persisted even after removal; one eye was explanted due to poor visual acuity with no haze formation. All patients experienced decreased unaided and corrected distance visual acuity. Persistent increase in corneal thickness and mean keratometry was noted post-explantation. All four patients regained their original near visual acuities, but one patient had persistent one-line loss in CDVA. There are long lasting tomographic corneal changes following Raindrop inlay explantation. In addition, persistent increased corneal thickness could be related to semi-permanent changes in corneal structure and may account for residual haze experienced by patients. After explantation, patients may not return to baseline CDVA.

KEYWORDS

Raindrop Corneal Inlay; Explantation; Presbyopia; Visual Prognosis; Corrected Distance Visual Acuity

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INTRODUCTION

The Raindrop® Near Vision Inlay (ReVision, Inc., Denver, CO, USA) received US FDA approval for use in the United States on June 29, 2016 after being determined to have reasonable safety and efficacy [1]. The Raindrop® inlay is a transparent microscopic hydrogel-based corneal inlay

(2millimeter [mm] diameter, 32micrometer [μm] thick, placed between 100-200μm depth) [2] designed to create a prolate-shaped cornea to correct near visual acuity in the non-dominant eye (Fig. 1). The insertion of the inlay into the central corneal stromal bed increases



stromal volume, which presses against the anterior cornea leading to an increase in central corneal curvature. This curvature change increases the refractive power of the central cornea by a few diopters, providing enhanced near visual acuity in presbyopic patients with the goal of improved distance and near visual acuity relying on the principle of monovision [2]. This product is no longer distributed in the United States after an FDA safety warning issued in 2018 due to corneal haze [3, 4]. One study found that adverse events generally took place in one of two periods, with the first occurring in the first 3 months postoperatively. Common adverse reports during this period were flap-related issues, pressure spikes, and inlay exchanges. The second period, from 3 months through 1 year, concerned mainly issues with inlay explants and transitory loss of corrected distance visual acuity; a small percentage of patients were reported to have central stromal haze during this period [5]. In addition, the more recent FDA report suggests that haze occurring after one year is a significant reason for explantation [4]. The purpose of this study is to highlight outcomes of patients who underwent Raindrop explantation. Data presented as mean, frequency, and percentage.

METHODS

This is a retrospective case series of patients who underwent Raindrop inlay implantation at our facility between December 2016 and April 2017. Inclusion criteria for implantation were: age 41-65, manifest refractive spherical equivalent +1.00 to -0.5 diopters (D) and ≤ 0.75 D cylindrical refraction, requiring +1.50 to +2.50 D for near vision [6]. Charts of patients who underwent explantation between December 2017 and April 2019 were reviewed. Information was collected on pre-implantation, pre-explantation, and post-explantation values for uncorrected near visual acuity (UNVA), uncorrected distance visual acuity (UDVA), and best corrected distance visual acuity (CDVA). Keratometric data on central corneal thickness (CCT) and mean keratometry (Km) was obtained from the Pentacam system (Oculus, Inc. Arlington, WA, USA). Approval was obtained from the Hoopes Research Committee, and informed consent was signed by each patient. All procedures adhered to the tenets of the Declaration of Helsinki.

RESULTS

Eight patients had Raindrop implantation during the study period. Four patients (50%) had subsequent explantation. The mean duration of implantation was 1.5 years (range 1 to 2.5 years) with a mean flap thickness of

175 μm (range 170-180 μm). The most recent data available was, on average, 242 days post-explantation (range 8-356 days). All four patients complained of blurry vision. Two patients complained of discomfort while the inlay was in place; both reported resolution of discomfort within weeks of explantation. Three patients complained of “seeing shadows” while the inlay was in place. Three patients had stromal haze that developed during implantation and persisted after explantation (Fig. 2). The haze resolved at the 1-year post-explantation follow up in two of the patients (duration of inlay implantation 16 and 17 months, respectively). The third patient with persistent haze has not completed a 1-month post-explantation exam (inlay was in place for 28 months). Out of the four eyes, only one patient did not experience haze during implantation or after removal; this patient’s inlay was in place for 12 months.

All patients regained or improved in UNVA compared to the pre-implantation value (mean increase 1.5 lines, Snellen) (Table 1). Uncorrected distance visual acuity changes ranged from 0-6 lines lost (mean loss of 4 lines, Snellen). Data on CDVA post-explantation was available in three out of four patients; one patient had persistent one-line loss of CDVA on last follow up (Table 1). No hyperopic shifts were recorded at any point during implantation. Mean keratometry had a mean increase of +2.5 D after implantation (Table 2). Manifest refraction spherical equivalent (MRSE) on all four patients showed a myopic shift before removal with mean decrease of -0.75 D; there was a persistent myopic shift compared to baseline in all three patients that had post-explantation MRSE (mean -0.46 D) (Table 3).

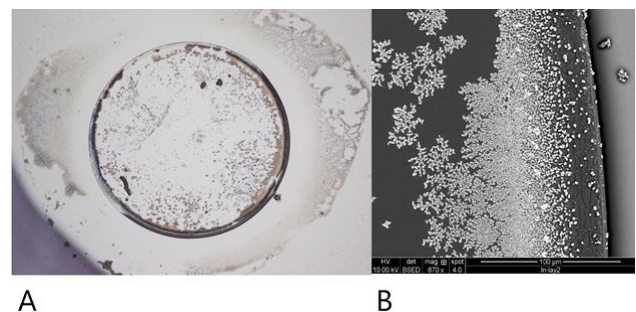


Figure 1: A: Light microscopy of explanted Raindrop® inlay, explanted from case 1 at 20x magnification. The specimen appears to be quite intact. Note that the deposits appear to be mostly related to the balanced salt solution as they are also observed on the glass slide outside of the area of the device. B: Scanning electron microscopy photograph of the inlay, showing the fern-like deposits on its surface.

Central corneal thickness had a mean increase of 27 μm after implantation. Keratometric and tomographic data was available post-explantation in two patients with a



Km increase of + 0.7 D and an increased CCT of 10-16 μm compared to pre-implantation (Table 2; Fig. 3).

Densitometry was done using the Pentacam system on patient 1 and showed an increase of 19.9 standard gray scale units (GSU) over 13 months of implantation. The density decreased by 25.0 GSU 8 months after removal (Fig. 4). Upon explantation, the inlay was placed on a glass slide and allowed to dry at room temperature. It was then forwarded to the Intermountain Ocular Research Center (University of Utah) for laboratorial analysis. Evaluation under a light microscope (Olympus Optical Co., Ltd.) (Fig. 1) showed the presence of deposits on the inlay, with a fern-like morphology that appeared to correspond to dried salts.

The specimen (inlay on glass slide) was then coated with gold-palladium, and then analyzed under scanning electron microscopy (SEM - Quanta 600F, ThermoFisher Scientific), coupled with energy dispersive spectroscopy (EDS) for elemental analysis of the deposits. The analyses were done under high vacuum pressure (approximately 10⁻⁶ torr), at room temperature, and an accelerating voltage of approximately 10-15 kV. SEM/EDS confirmed that the deposits on the inlay were mostly composed of sodium (Na) and chlorine (Cl).

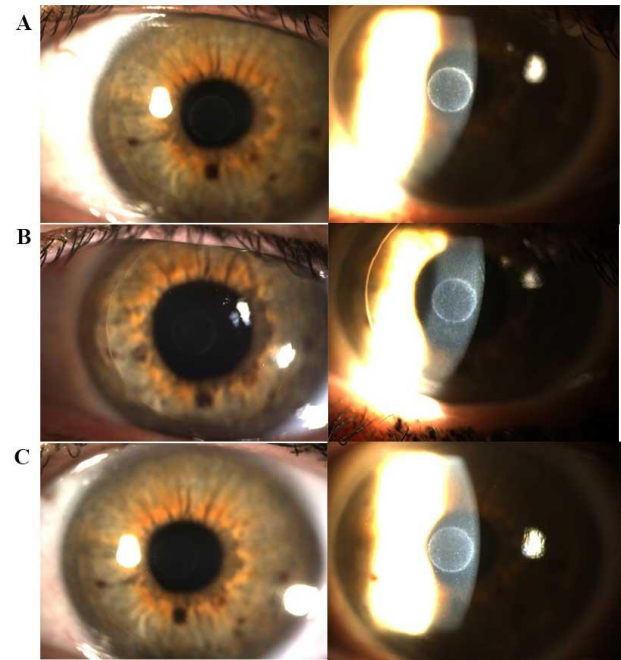


Figure 2: Photographs of case 1 taken immediately before (A), 1 day after (B), and 1 month after (C) explantation of the Raindrop® corneal inlay. Note that the haze appears to be subsiding slightly in the more direct lighting conditions but lingers with the tangential illumination. The observer may mistakenly believe the inlay is still in place when it is in fact explanted and there is only residual haze and fibrosis.

Table 1: Changes in Visual Acuity Pre- and Post-explantation of the Raindrop® Hydrogel Corneal Inlay.

Patients	UDVA			UNVA			CDVA		
	Pre-inlay	Pre-explant	Post-explant	Pre-inlay	Pre-explant	Post-explant	Pre-inlay	Pre-explant	Post-explant
1	20/25	20/300	20/80	20/100	20/40	20/63	20/20	20/40+2	20/25+
2	20/20	20/25	20/20-	20/50	20/40	20/50	20/20	20/25+2	20/20-
3	20/20	20/70-2	20/40+2	20/100	20/50	20/100	20/20	20/25-	20/20
4	20/20-2	20/50	20/50	20/100	20/80	20/100	20/20	20/40	NA

Abbreviations: CDVA: corrected distance visual acuity; UDVA: uncorrected distance visual acuity; UNVA: uncorrected near visual acuity; NA: not available; Pre-inlay: before implantation of inlay; Pre-explant: before explantation of inlay; Post-explant: after explantation of inlay

Table 2: Changes in keratometry and CCT Pre- and Post-explantation of the Raindrop® Hydrogel Corneal Inlay.

Patients	Pre-Implantation		Pre-explantation		Post-explantation	
	Km(D)	CCT (μm)	Km(D)	CCT (μm)	Km(D)	CCT (μm)
1	43	537	45.2	554	43.7	555
2	45	554	45.2	565	NA	NA
3	43.2	580	48.8	632	43.9	596
4	42.4	559	44.4	586	NA	NA

Abbreviations: Km: mean keratometry; CCT: central corneal thickness; D: diopter; μm : micrometer; NA: not available

Table 3: Changes in manifest refraction Pre- and Post-explantation of the Raindrop® Hydrogel Corneal Inlay

Patient	MRSE (D) Pre-implantation	MRSE (D) Pre-explantation	MRSE (D) post-explantation	Change from baseline
1	-0.375	-1.75	-1.375	-1
2	-0.125	-0.25	-0.25	-0.125
3	+0.75	-0.125	+0.5	-0.25
4	+0.5	-0.125	NA	NA

Abbreviations: MRSE: manifest refraction spherical equivalent; D: diopter; NA: not-available.

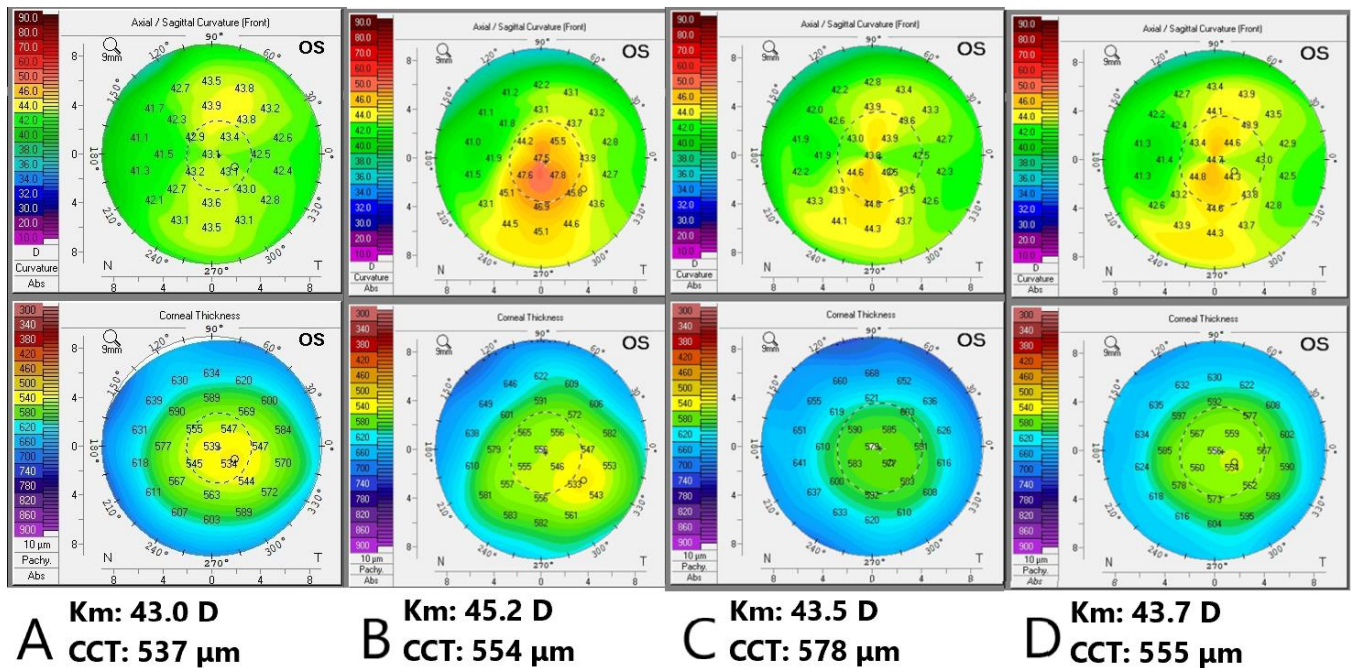


Figure 3: PENTACAM data for case 1 of the Raindrop® Hydrogel Corneal Inlay.

A) shows pre-implantation data, with a Km of 43.0 D and CCT of 537 μ m. B) shows pre-explantation data with a Km of 45.2 D and CCT of 554 μ m. C) shows 1-day post-explantation data with a Km of 43.5 and CCT of 578 μ m. D) shows 1-month post-explantation data with a Km of 43.7 and CCT of 555 μ m. Abbreviations: Km: mean keratometry; D: diopter; CCT: Central corneal thickness; μ m: micrometer.

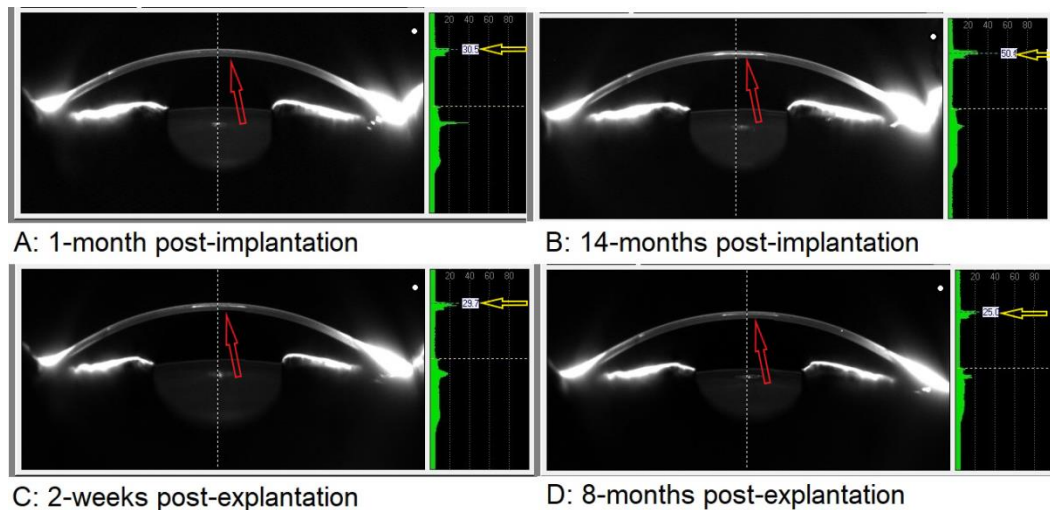


Figure 4: Densitometry from PENTACAM for case 1 of the Raindrop® Hydrogel Corneal Inlay at various time-points.

Red arrows point to corneal stromal haze and yellow arrows point to the corresponding densitometry measurement. Densitometry values were as follows: 30.5 grayscale units (GSU) at 1-month post-implantation; 50.4 GSU at 14-months post-implantation; 29.7 GSU at 2-weeks post-explantation; and 25.0 GSU at 8-months post-explantation. Density increases with the duration of implantation. After explantation, density decreases with time. We infer that the increase in density correlates with corneal haze.

DISCUSSION

The results of this case series highlight reasons for the high explantation rate of the Raindrop and visual prognosis after removal. There appeared to be no changes to the inlay over the course of implantation. Haze was a very common problem and was persistent up

to 1 year after explantation. Tomography and keratometry demonstrated corneal shape changes induced by the inlay; these changes persisted to some degree after explantation.

Garza et al. reported a case of explantation due to unsatisfactory visual outcomes [7]. Chayet et al. reported another case of explantation that occurred in a patient



that had LASIK post-inlay implantation and experienced haze [8]. In the FDA post-approval study for Raindrop, there is a 23% explant rate over 5 years [4].

Normal density values (for eyes without history of corneal inlay) based on densitometry measurements are reported to be around 20 GSU [9]. Our data showed an increase in density with duration of implantation (Fig. 4). We postulate that corneal haze and increased density may be secondary to inflammatory changes induced by the implant. Both haze and density decreased over months after removal. Resolution of haze may occur through the cornea's restorative mechanisms. This includes epithelial healing via limbal stem cells, basement membrane remodeling, and stromal healing via keratocyte motility and Transforming growth factor beta (TGF-beta) activation [10]. Densitometry has been used to monitor haze in other patients with a corneal inlay [11]. We suggest that densitometry is a more objective way to measure haze-related changes induced by corneal inlays. The long-term recoverability of these impacted corneas remains to be seen, and additional studies should be conducted to investigate this phenomenon.

Corneal tomography showed an expected Km increase after implantation. However, Km and CCT were persistently elevated even after explantation, demonstrating that there were residual changes in corneal shape. This could explain why two of the patients still maintained better UNVA even after inlay removal. Despite these changes, all tomographic values trended toward baseline on latest follow-up (Table 2; Fig. 3). Longer follow up is needed to determine if corneal shape will return to baseline after inlay removal.

As a point of comparison, the KAMRA® inlay also has studies on its explantation [12, 13]. A recent study of KAMRA® explantation from Shing Ong et al. found that one major complication during implantation was corneal haze and accompanying hyperopic refractive shifts [12]. It was also found that after explantation the vision trended back toward baseline values and the authors concluded that early removal led to better visual outcomes [12]. Haze was a similar reason for explantation of the Raindrop, although hyperopic shifts were not reported in our series. Both inlays trend toward baseline values after removal. However, the method of insertion – flap insertion (Raindrop®) and pocket insertion (KAMRA®), the insertion depth, and the mechanism of action differ significantly between the two inlays.

There were several limitations to this study. First, there was a very small sample size. The study was retrospective in nature and limited by the amount of information

available in the chart. Follow up times varied widely, with minimal post-explantation data available on one patient. Perhaps a larger sample size with more consistent follow up could bring greater insight to factors associated with development and resolution of haze. If more patients had data available on tomography and densitometry, more robust conclusions could be made as to the changes induced by the Raindrop corneal inlay.

CONCLUSION

Despite the small sample size and retrospective nature of the study, we conclude that the Raindrop is associated with significant adverse effects, the most common being blurry vision and stromal haze. Because of the small sample size, it is difficult to establish a temporal relationship between haze development and resolution. Persistent shape changes may account for improvement of UNVA after removal, but deficits in UDVA are common with potential for persistent loss of CDVA. In addition, tomographic and density changes persisted post-explantation (Figs. 3 and 4). Patients should not expect to return to pre-implantation values in the short term after removal. As per FDA advice, patients with Raindrop implants should follow-up regularly, even after explantation, due to the development of corneal haze [4]. Alternative synthetic inlays other than the Raindrop® exist [7, 14-20]. However, allogenic implants such as the presbyopic allogenic refractive lenticule (PEARL) [21] and TransForm corneal allograft (TCA) [22] are undergoing clinical trials. Perhaps using an allogenic implant will result in a lower complication rate and will not induce as visually-disturbing corneal haze as synthetic inlays such as the Raindrop.

DISCLOSURE

Ethical issues have been completely observed by the authors. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship of this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval for the version to be published. No conflict of interest has been presented. Phillip C Hoopes Jr, MD is a consultant for CorneaGen.

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REFERENCES

1. PMA P150034: FDA Summary of Safety and Effectiveness Data (SSED): 1-49. 2016. Available from: <https://www.fda.gov/media/123081/download>.
2. ReVision Optics Inc. Raindrop® Near Vision Inlay Professional Use Information. 2017 [cited 2017 March]. Available from: https://www.accessdata.fda.gov/cdrh_docs/pdf15/p150034c.pdf.
3. Hovanesian J. ReVision Optics goes out of business. 2018 [cited 2018 Feb 1st]. Available from: <https://www.healio.com/ophthalmology/ophthalmic-business/news/online/%7Bcbdd13e9-f879-4516-96c9-b096a30193af%7D/revision-optics-goes-out-of-business>.
4. FDA. Increased Risk of Corneal Haze Associated with the Raindrop Near Vision Inlay: FDA Safety Communication [cited 2019 May 29]. Available from: <https://www.fda.gov/medical-devices/safety-communications/increased-risk-corneal-haze-associated-raindrop-near-vision-inlay-fda-safety-communication>.
5. Whitman J, Dougherty PJ, Parkhurst GD, Olkowski J, Slade SG, Hovanesian J, et al. Treatment of Presbyopia in Emmetropes Using a Shape-Changing Corneal Inlay: One-Year Clinical Outcomes. *Ophthalmology*. 2016;123(3):466-75. doi: 10.1016/j.ophtha.2015.11.011 pmid: 26804761
6. RAINDROP®Near Vision Inlay Professional Use Information [cited 2019 May 17]. Available from: www.raindropinlay.com.
7. Garza EB, Gomez S, Chayet A, Dishler J. One-year safety and efficacy results of a hydrogel inlay to improve near vision in patients with emmetropic presbyopia. *J Refract Surg*. 2013;29(3):166-72. doi: 10.3928/1081597X-20130129-01 pmid: 23446012
8. Chayet A, Barragan Garza E. Combined hydrogel inlay and laser in situ keratomileusis to compensate for presbyopia in hyperopic patients: one-year safety and efficacy. *J Cataract Refract Surg*. 2013;39(11):1713-21. doi: 10.1016/j.jcrs.2013.05.038 pmid: 24021565
9. Ni Dhubghaill S, Rozema JJ, Jongenelen S, Ruiz Hidalgo I, Zakaria N, Tassignon MJ. Normative values for corneal densitometry analysis by Scheimpflug optical assessment. *Invest Ophthalmol Vis Sci*. 2014;55(1):162-8. doi: 10.1167/iovs.13-13236 pmid: 24327608
10. Ljubimov A, Saghizadeh M. Progress in corneal wound healing. *Prog Retin Eye Res*. 2016;49(310):17-45. doi: 10.1016/j.preteyeres.2015.07.002
11. Chu R, Lee BR. Diagnostic and Management Tool for Monitoring Patients Implanted with a Shape-Changing Corneal Inlay. *Case Rep Ophthalmol*. 2018;9(1):190-6. doi: 10.1159/000484436 pmid: 29681835
12. Ong HS, Chan AS, Yau CW, Mehta JS. Corneal Inlays for Presbyopia Explanted Due to Corneal Haze. *J Refract Surg*. 2018;34(5):357-60. doi: 10.3928/1081597X-20180308-01 pmid: 29738595
13. Amigo A, Martinez-Sorribes P, Recuerda M. Late-onset refractive shift after small-aperture corneal inlay implantation. *J Cataract Refract Surg*. 2018;44(5):658-64. doi: 10.1016/j.jcrs.2018.03.029 pmid: 29891159
14. Lang AJ, Holliday K, Chayet A, Barragan-Garza E, Kathuria N. Structural Changes Induced by a Corneal Shape-Changing Inlay, Deduced From Optical Coherence Tomography and Wavefront Measurements. *Invest Ophthalmol Vis Sci*. 2016;57(9):OCT154-61. doi: 10.1167/iovs.15-18858 pmid: 27409467
15. Tomita M, Kanamori T, Waring GOt, Nakamura T, Yukawa S. Small-aperture corneal inlay implantation to treat presbyopia after laser in situ keratomileusis. *J Cataract Refract Surg*. 2013;39(6):898-905. doi: 10.1016/j.jcrs.2013.01.034 pmid: 23688876
16. Tomita M, Kanamori T, Waring GOt, Yukawa S, Yamamoto T, Sekiya K, et al. Simultaneous corneal inlay implantation and laser in situ keratomileusis for presbyopia in patients with hyperopia, myopia, or emmetropia: six-month results. *J Cataract Refract Surg*. 2012;38(3):495-506. doi: 10.1016/j.jcrs.2011.10.033 pmid: 22340607
17. Limnopoulou AN, Bouzoukis DI, Kymionis GD, Panagopoulou SI, Plainis S, Pallikaris AI, et al. Visual outcomes and safety of a refractive corneal inlay for presbyopia using femtosecond laser. *J Refract Surg*. 2013;29(1):12-8. doi: 10.3928/1081597X-20121210-01 pmid: 23311737
18. Moshirfar M, Desautels JD, Wallace RT, Koen N, Hoopes PC. Comparison of FDA safety and efficacy data for KAMRA and Raindrop corneal inlays. *Int J Ophthalmol*. 2017;10(9):1446-51. doi: 10.18240/ijo.2017.09.18 pmid: 28944206
19. Malandrini A, Martone G, Menabuoni L, Catanese AM, Tosi GM, Balestrazzi A, et al. Bifocal refractive corneal inlay implantation to improve near vision in emmetropic presbyopic patients. *J Cataract Refract Surg*. 2015;41(9):1962-72. doi: 10.1016/j.jcrs.2015.01.018 pmid: 26603405
20. Moarefi MA, Bafna S, Wiley W. A Review of Presbyopia Treatment with Corneal Inlays. *Ophthalmol Ther*. 2017;6(1):55-65. doi: 10.1007/s40123-017-0085-7 pmid: 28390052
21. Jacob S, Kumar DA, Agarwal A, Agarwal A, Aravind R, Saijimal AI. Preliminary Evidence of Successful Near Vision Enhancement With a New Technique: PrEsbyopic Allogenic Refractive Lenticule (PEARL) Corneal Inlay Using a SMILE Lenticule. *J Refract Surg*. 2017;33(4):224-9. doi: 10.3928/1081597X-20170111-03 pmid: 28407161
22. Allotex. The Natural Solution for Vision Correction [cited 2019 May 28]. Available from: <https://allotex.com/science/clinical-data/>.